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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,773	01/16/2004	Seng H. Cheng	07680.0018	6298

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
05/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,773	CHENG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,14-18,20,37,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,14-18,20,37,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-26-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 2-26-09 has been entered. Claims 1 and 20 have been amended. Claims 4, 7-12, 22, 36, 38 and 42-47 have been canceled. Claims 1, 3, 6, 14-18, 20, 37, 40 and 41 are pending and under consideration.

Priority

Application No. 09/884,526, filed 6-19-01, failed to disclose the subject matter of using tissue-specific promoter or liver-specific promoter (independent claim 1) or using human albumin promoter and human prothrombin enhancer (independent claim 20) in gene therapy vector for treating Fabry disease. Therefore, the priority dates of 09/884,526 and 60/212,377 are NOT granted. The effective priority date of the instant invention is the filing date of the invention, i.e. 1-16-04.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 3, 6, 14-18, 20, 37, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiffmann et al., January 2000 (PNAS, Vol. 97, No. 1, p. 365-370) and Jung et al., 2001 (PNAS, Vol. 98, No. 5, p. 2676-2681, IDS) in view of Ziegler et al., 2001 (US 20010031741 A1) and Souza et al., 2007 (US Patent No. 7,312,324 B2). Applicants' amendment filed 2-26-09 necessitates this new ground of rejection.

The claims are directed to a method of reducing globotriaosylceramide (GL-3) in a subject with Fabry disease, comprising first administering an AAV vector encoding alpha-galactosidase A under the control of at least one liver-specific regulatory element, such as liver-specific promoter or enhancer, and then administering exogenously produced alpha-galactosidase A protein, and the method results in a decrease in GL-3 in the subject, or a method of reducing GL-3 in a subject having Fabry disease comprising first administering a gene therapy vector encoding alpha-galactosidase A under the control of a human albumin promoter and 2 copies of a human prothrombin enhancer and then administering an exogenously produced natural or recombinant alpha-galactosidase A, wherein the GL-3 level is decrease in said subject. Claims 6 and 37 specify less amount of the exogenously produced alpha-galactosidase A is administered to the subject than would be administered if the subject had not been administered a gene therapy vector encoding the alpha-galactosidase A or without a liver-specific regulatory element. Claims 14 and 40 specify the viral vector is AAV1, AAV2, AAV5, AAV7 or AAV8. Claims 15 and 16 specify the liver-specific regulatory element is a liver-specific promoter and a human serum

albumin promoter, respectively. Claims 17 and 18 specify the liver-specific regulatory element is a liver-specific enhancer and a human prothrombin enhancer, respectively. Claim 41 specifies the liver-specific regulatory element is DC190 (a human albumin promoter and 2 copies of a human prothrombin enhancer).

Schiffmann et al., January 2000 (PNAS, Vol. 97, No. 1, p. 365-370) teaches i.v. infusion of purified alpha-galactosidase A (alpha-gal A) enzyme into patient results in distribution of the enzyme in several cell types, including sinusoidal endothelial cells, Kupffer cells, and hepatocytes, and globotriaostlceramide (Gb3) levels are significantly reduced in the liver and shed renal tubular epithelial cells in the urine sediment.

Jung teaches that Fabry disease is a lysosomal storage disease caused by a deficiency of alpha-galactosidase A (alpha-gal A) and delivery of the normal alpha-galactosidase A cDNA into a depot organ such as liver may be sufficient to elicit corrective circulating levels of the deficient enzyme. Jung teaches injecting an AAV vector expressing human alpha-gal A under the control of human EF-1-alpha promoter (rAAV-AGA) into the hepatic portal vein of Fabry mice and shows higher alpha-gal A levels in liver and other tissue as compared to control and, in parallel to the elevated enzyme level, significant reduction in Gb3 (GL-3) levels in liver, spleen and heart up to 25 weeks posttreatment (e.g. abstract, p. 2676, right column, 3rd full paragraph). "Liver by far showed the most impressive correction at 2, 5, 15 and 25 weeks … compared with age-matched Fabry mice that did not get the treatment" (e.g. p. 2678, right column, 1st full paragraph).

Schiffmann and Jung do not specifically teach using liver specific regulatory sequence, such as DC190, in gene therapy vector or combination of gene therapy and enzyme therapy, and

less amount of the exogenously produced alpha-galactosidase A is needed in combination therapy when compared to enzyme replacement therapy alone.

Ziegler teaches "the methods of the present invention may allow for more effective treatment of lysosomal storage diseases using enzyme replacement therapy and/or gene therapy in which lower dosage regimens may conveniently be used" ([0013]).

Souza teaches combining promoter elements that have the potential to direct effective and sustained expression with liver specific enhancer element to achieve high and sustained transgene expressin in liver. The promoter elements include human serum albumin promoter and alpha-1-antitrypsin promoter, and the enhancer elements include HAS enhancers, a human prothrombin enhancer and an alpha-1-microglobulin enhancer (e.g. column 6, 2nd full paragraph). Souza also teaches a DNA vector comprising a human serum albumin promoter and two human prothrombin enhancers (e.g. claim1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to combine gene therapy and enzyme therapy in reducing GL-3 level in a subject having Fabry disease because Ziegler teaches combining gene therapy and enzyme replacement therapy for more effective treatment of lysosomal storage diseases in which lower dosage regimens may conveniently be used and Fabry disease is one type of lysosomal storage diseases and reducing GL-3 level is one object of treating Fabry disease as evidenced by Jung. Further, administering gene therapy vector first and then administering enzyme in treating Fabry disease would be obvious to one of ordinary skill because determining the order of administering gene therapy vector and enzyme would be routine optimization in order to obtain the most effective procedure to treat Fabry disease. It also would have been prima facie obvious to one of ordinary

skill in the art to use liver specific regulatory elements in gene therapy vector because Souza teaches using liver specific promoter, such as human serum albumin promoter, and liver specific enhancer, such as human prothrombin enhancer, to achieve high and sustained transgene expression in liver and Jung teaches delivery of the normal alpha-gal A cDNA into a depot organ such as liver may be sufficient to elicit corrective circulating levels of the alpha-gal A. Ziegler teaches that lower dosage regimes may be used when using gene therapy and enzyme replacement therapy, therefore, it would be obvious to one of ordinary skill that less amount of alpha-galactosidase A is needed in combination therapy when compared to enzyme replacement therapy alone.

One having ordinary skill in the art at the time of the invention would have been motivated to do so in order to reduce the level of GL-3 (or Gb3) in Fabry disease patient as taught by Schiffmann and Jung with reasonable expectation of success.

Applicants argue that Office has not provided any basis or reference to support that the primary target tissue in treating Fabry disease is liver (amendment, p. 9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection. Jung teaches that delivery of the normal alpha-gal A cDNA into a depot organ such as liver may be sufficient to elicit corrective circulating levels of the alpha-gal A. It is apparent that liver is the primary organ for treating Fabry disease to reduce the GL-3 level in a patient.

Conclusion

No claim is allowed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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